1. NAME OF THE MEDICINAL PRODUCT

LIDOCADREN TEVA® Solution for injection
Lidocaine hydrochloride + Epinephrine (Adrenaline)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains:

Lidocaine hydrochloride	20.0 mg
Epinephrine (adrenaline)	0.0125 mg
(Equivalent to 0.02275 Epinephrine tartrate)	

Excipients:

Sodium chloride	5.80 mg
Sodium metabisulphite	0.55 mg

1 cartridge (1.8 ml) contains 36 mg of lidocaine hydrochloride (2%) and 0.0225 mg of epinephrine ([equivalent to 0.04095 mg of epinephrine tartrate] [1:80,000]).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection, clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Production of local anaesthesia by nerve-block infiltration technique.

4.2 Posology and method of administration

LIDOCADREN TEVA is intended for use in adults, adolescents and children above 4 years of age.

Posology
The dosage should be adjusted individually according to the area to be anaesthetised, vascularisation of the tissues and anaesthetic technique to be used.

The recommended doses according to the technique used are described in the table below.

Anaesthetic technique	Recommended dose	Adults (70 kg)	Children	
			20 kg-child	40 kg-child
Infiltrations or terminal anaesthesia	in ml of solution	1 ml	0.3 ml	0.6 ml
	in mg of lidocaine HCl	20 mg	6 mg	12 mg
Truncal anaesthesia	in ml of solution	1.5 – 2 ml	0.4 – 0.6 ml	0.8 – 1 ml
	in mg of lidocaine HCl	30 – 40 mg	8 – 12 mg	16 – 20 mg

Maximum dose
Adults:
The maximum dose over a period of 24 hours is 490 mg of lidocaine (for a person of 70 kg), which must not exceed 7 mg/kg of body weight in adults.

Children:
The dose will be adjusted according to the patient's age and weight, as well as the type of surgery to be performed, not exceeding 5 mg/kg of body weight.
The use of LIDOCADREN TEVA is contraindicated in children under 4 years of age.

Lidocadren TEVA is indicated for use in adults and in children older than 4 years of age. The amount to be injected should be determined by the age and weight of the child and the scale of the operation. The anaesthetic technique must be carefully selected. Painful anaesthetic techniques should be avoided. The behaviour of children must be monitored carefully during treatment. The mean dose for use is in the range 20 mg to 30 mg lidocaine hydrochloride per session. Alternatively, the dose in mg of lidocaine hydrochloride that can be administered in children can be calculated using the expression: weight of child (in kilogrammes) x 1.33. Do not exceed the equivalent of 5 mg lidocaine hydrochloride per kilogramme body weight.

Special population:
Increased plasma levels of LIDOCADREN TEVA can occur in older patients due to diminished metabolic processes and lower distribution volume.

The risk of accumulation of LIDOCADREN TEVA is increased in particular after repeated application. A similar effect can ensue from severely impaired hepatic function (see section 4.4.), thus a lower dose is recommended in these cases.

Method of administration
For injection/oromucosal use.
For use in dental anaesthesia only.
To avoid intravascular injection, aspiration control at least in two planes (rotation of the needle by 180°) must always be carefully undertaken. The injection rate should not exceed 0.5 ml in 15 seconds, i.e. 1 cartridge per minute.

4.3 Contraindications

LIDOCADREN TEVA is contraindicated in case of hypersensitivity to the active ingredients or any other of the components.
The use of LIDOCADREN TEVA is contraindicated in children younger than 4 years of age.

Due to the content in lidocaine, LIDOCADREN TEVA is contraindicated in case of:

- known allergy or hypersensitivity to local anaesthetics of the amide type
- severe disorders of atrioventricular conduction not compensated by a pacemaker.
- deficiency in plasma cholinesterase activity
- severe blood coagulation dysfunction
- degenerative nervous disorders

Due to the content in epinephrine (adrenaline); LIDOCADREN TEVA is contraindicated in case of:

- Unstable angina pectoris.
- Recent myocardial infarction.
- Recent coronary artery bypass surgery.
- Refractory arrhythmias and paroxistic or high rate tachycardia, continuous arrhythmia.
- Severe untreated or uncontrolled hypertension.
- Untreated or uncontrolled congestive heart failure.
- Concomitant treatment with monoamine oxidase (MAO) inhibitors or tricyclic antidepressants (see section 4.5).

Due to the content in metabisulphite, LIDOCADREN TEVA is contraindicated in case of:

- Allergy or hypersensitivity to sulphite.
- Severe bronchial asthma.

4.4 Special warnings and precautions for use

Warnings
Inadvertent intravascular injection may be associated with convulsions, followed by central nervous system or cardiorespiratory arrest. Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use.

To minimize the likelihood of intravascular injection, aspiration should be performed before the local anesthetic solution is injected. If blood is aspirated, the needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not assure that intravascular injection will be avoided.

It should be taken into consideration that during treatment with blood coagulation inhibitors (e.g. heparin or acetylsalicylic acid), an inadvertent vasopuncture when administering the local anaesthetic can lead to serious bleeding, and the hemorrhagic tendency may be increased (see section 4.5).

Athletes should be warned that this medicinal product contains an active substance likely to yield a positive result in anti-doping tests.

The injection of this medicinal product must be avoided in infected area.

The patient must be warned of the possibility of injuries due to involuntary biting of the lips, tongue and buccal mucosa while these structures are anaesthetised. Consequently, food intake must be postponed until sensitivity returns.

The presence of sodium metabisulphite as an excipient may cause allergic reactions, including anaphylactic-type reactions and bronchospasm in susceptible patients, particularly those with an asthmatic or allergic history.

This medicinal product contains less than 1 mmol sodium (23 mg) per 1 ml, i.e., essentially sodium-free.

Precautions for use

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical condition.

If sedatives are employed to reduce patient apprehension, reduced doses should be used since local anesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect. Young children should be given minimal doses of each agent. Lidocaine should be used with caution in patients with severe shock or heart block.

The product should be administered with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of atrioventricular conduction produced by these drugs (see section 4.3).

Local anesthetic solutions containing a vasoconstrictor should be used with caution in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions.

LIDOCADREN TEVA should be used with precaution in patients with:

- angina pectoris
- arteriosclerosis
- impaired blood coagulation
- diabetes mellitus
- severe hepatic impairment. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations.
- lung diseases – particularly allergic asthma
- epilepsy
- phaeochromocytoma
- narrow-angle glaucoma
- thyrotoxicosis
- Acute porphyria LIDOCADREN TEVA is probably porphyrinogenic and should only be prescribed to patients with acute porphyria on strong or urgent indications. Appropriate precautions should be taken for all porphyric patients

Cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be monitored after each local anesthetic injection. Restlessness, anxiety tinnitus, dizziness, blurred vision, tremors, depression or drowsiness should alert the practitioner to the possibility of central nervous system toxicity. Signs and symptoms of depressed cardiovascular function may commonly result from a vasovagal reaction, particularly if the patient is in an upright position; placing the patient in the recumbent position is recommended when an adverse response is noted after injection of a local anesthetic.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction, and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspected triggering agent (s) and prompt treatment, including oxygen therapy, dantrolene (consult dantrolene sodium intravenous package insert before using) and other supportive measures. Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Use in the Head and Neck Area
Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported.

These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its content in lidocaine, LIDOCADREN TEVA should be used with caution in patients that receive concomitant medication similar in structure to local anaesthetics (for example, Ib-class antiarrhythmic drugs), since the toxic effects are additive.

Due to its content in epinephrine, LIDOCADREN TEVA should be administered with caution in patients who are simultaneously receiving one of the following medications:

- Blood coagulation inhibitors (heparin), nonsteroidal anti-inflammatory drugs (NSAID), plasma substitutes (dextran), phenotiazines, butyrophenones: these drugs may reduce or reverse the vasopressor effect of epinephrine possibly causing hypotension, tachycardia and an increased haemorrhagic tendency.

- Tricyclic antidepressants, monoamine oxidase inhibitors (MAOI), ergotamine-like oxytocic drugs, non-selective beta blockers like propanol: these drugs may increase the vasopressor effect of epinephrine and may lead to serious hypertension and bradycardia.

4.6 Pregnancy and lactation

Pregnancy
Even if there is no evidence from animal studies of harm to the foetus, LIDOCADREN TEVA should not be given during pregnancy unless strictly necessary.

The administration of LIDOCADREN TEVA during pregnancy may cause foetal bradycardia due to its content in local anaesthetic, as well as a decrease in intrauterine blood flow due to its content in epinephrine, especially in case of inadvertent intravascular injection.

Lactation

Lidocaine may enter the mother's milk, but in such small amounts that there is generally no risk of this affecting the neonate. It is not known whether adrenaline enters breast milk or not, but it is unlikely to affect the breast-fed child. Thus, it is considered that LIDOCADREN TEVA may be used during lactation.

Pediatric use

Dosages in pediatric population should be reduced, commensurate with age, body weight and physical condition.

4.7 Effects on ability to drive and use machines

Depending on the dose and site of administration, local anaesthetics may affect mental functions and temporarily alter locomotion and coordination. When administering this medicine, the doctor or dentist must evaluate in each particular case whether the ability of the patient to react has been compromised and whether the patient can drive or use machines. The patient must remain in the consulting room for at least 30 minutes after the intervention.

4.8 Undesirable effects

Adverse effects strictly attributable to the local anaesthetic are limited. However, the physiological effects from nerve block are frequent, but these vary considerably depending on what type of block is administered.

The following adverse reactions can occur as a result of the content of lidocaine as local anaesthetic:

FREQUENCY	**DISORDERS**	**EFFECTS**
Rare (≥1/10,000 to <1/1000)	Cardiac disorders	Hypotension, arrhythmias, bradycardia, cardiac arrest

	Nervous system disorders	Metallic taste, tinnitus, feeling of dizziness, nausea, vomiting, anxiety, tremors, nystagmus, headaches, increased breathing rate. Paraesthesia (numbness accompanied by a burning sensation) of the lip and/or tongue Unconsciousness and seizures, coma and respiratory arrest (in the event of overdose)
	Respiratory disorders	Tachypnoea followed by bradypnoea, possibly causing apnoea.
Very rare (< 1/10,000)	General disorders and administration site conditions	Allergic reactions, skin rash, erythema, pruritus, oedema of the tongue, mouth, lips or throat and, in the most severe cases, anaphylactic shock.

The following adverse reactions can occur as a result of the content of epinephrine as a vasoconstrictor:

FREQUENCY	**DISORDERS**	**EFFECTS**
Rare (≥1/10,000 to <1/1000)	Cardiac disorders	Hot sensation, sweating, migraine-type headaches, increased blood pressure, angina pectoris disorders, tachycardias, tachyarrhythmias, and cardiac arrest, as well as oedematous swelling of the thyroids.

The following adverse reactions can occur as a result of the content of metabisulfite as an excipient:

FREQUENCY	DISORDERS	EFFECTS
Very rare (< 1/10,000)	General disorders and administration site conditions	Particularly in bronchial asthmatics, allergic reactions which manifest as vomiting, diarrhoea, wheezing, acute asthma attack, clouding of the consciousness or anaphylactic shock may occur.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

4.9.1 Toxicity

Accidental intravascular injections of local anaesthetics may cause immediate systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15–60 minutes after injection). Toxicity is manifested first in the central nervous system, then followed by the cardiovascular system. In paediatric patients, when a local anaesthetic is administered under general anaesthesia, it is difficult to detect the first signs of toxicity to the local anaesthetic.

Central nervous system toxicity
Initially, symptoms include agitation, a feeling of intoxication, a sensation of numbness in the lips and tongue, paresthesias around the mouth, dizziness, vision and hearing disturbances, and buzzing in the ears. Speech problems, muscle stiffness and spasms are more serious symptoms and precede generalised seizures. Respiratory arrest may even occur in severe cases. Acidosis increases the toxic effects of local anaesthetics. Recovery depends on the metabolism of the local anaesthetic and the distribution away from the central nervous system. This occurs quickly providing large amounts of the drug are not injected.

Cardiovascular system
The symptoms associated to the local anaesthetic may include blood pressure drop, bradycardia, arrhythmia, and cardiac arrest as a result of high systemic concentrations of local anaesthetic.
The symptoms associated to epinephrine are heat sensation, sweating, heart rhythm acceleration, headaches, blood pressure increase, anginous disorders, tachycardia, tachyarrhythmia, and cardiac arrest.

4.9.2 Treatment

General basic measures
If adverse reactions arise the application of the local anaesthetic has to be stopped. Measures should focus on maintenance/restoration of the vital functions of respiration and circulation, oxygen administration and intravenous access.

Special measures
- Hypertension: Elevation of the upper body, if necessary sublingual nifedipine.
- Seizures: Protect patients from concomitant injuries, if necessary benzodiazepines (e.g. diazepam IV).
- Hypotension: Horizontal position, raise legs up, if necessary intravascular infusion of a complete electrolyte solution IV, vasopressors (e.g. ethylephrine IV).
- Bradycardia: Atropine IV.
- Anaphylactic shock: Infusion of a complete electrolyte solution, if necessary epinephrine IV, cortisone IV; contact emergency physician.
- Cardiovascular arrest: Immediate cardiopulmonary resuscitation, contact emergency physician.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local anaesthetics: amides, ATC code: N01BB52.

As other local anaesthetics, lidocaine reversibly blocks the propagation of the impulse along the nerve fibers, thus preventing the mobility of sodium ions through the nerve membrane.

At high doses lidocaine has a quinidine-like action on the myocardium, i.e., cardiac depressant. All local anaesthetics stimulate the central nervous system and may produce anxiety, restlessness and tremors.

The onset and duration of lidocaine action are increased by adding epinephrine as vasoconstrictor. Thus, the absorption of the anaesthetic is delayed and a greater concentration is obtained for a longer period. Also, the possibility of systemic adverse effects is reduced.

5.2 Pharmacokinetic properties

Absorption
The information obtained from different formulations, concentrations and uses shows that lidocaine is absorbed completely upon parenteral administration and that its absorb ration depends, for example, on various factors such as the site of administration and the presence or absence of a vasoconstrictor. Except for intravascular administration, the highest blood concentrations are obtained via intercostal nerve blockade and the lowest levels after subcutaneous administration.

Distribution
The binding of lidocaine to plasma proteins is dependent on the concentration of the drug and the bound fraction decreases with increasing concentration. At concentrations of between 1 and 4 µg free fraction per ml, between 60% and 80% of lidocaine is bound to proteins. Binding is also dependent on the plasma concentration of alpha-1-acid glycoprotein.

Lidocaine crosses the blood-brain barrier and placenta, supposedly by passive diffusion.

Biotransformation
Lidocaine is rapidly metabolised by the liver, with metabolites and non-metabolised drug being excreted via the kidneys. Biotransformation includes oxidative N-dealkylation, aromatic hydroxylation, cleavage of the amide bond and conjugation. N-dealkylation results in the monoethylglycinexylidide and glycinexylidide metabolites. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of the lidocaine administered is excreted in the form of various metabolites and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2,6-dimethylaniline.

Elimination
Studies of lidocaine metabolism after injection of an intravenous bolus have shown that the elimination half-life of this agent is between 1.5 and 2 hours. Due to the high metabolisation rate of lidocaine, any condition that affects hepatic function may alter lidocaine kinetics. The half-life may be prolonged twofold or more in patients with hepatic impairment. Renal impairment does not affect lidocaine kinetics but may increase the accumulation of metabolites.

5.3 Preclinical safety data

Non-clinical safety data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

As for other amide-type local anaesthetics, the active substance in high doses may cause reactions on the central nervous system and the cardiovascular system (see section 4.8. *Undesirable effects*).

A metabolite of lidocaine, 2,6-dimethylaniline, showed weak evidence of activity in some genotoxicity tests. The metabolite 2,6-dimethylaniline has been shown to have carcinogenicity potential in preclinical toxicological studies evaluating chronic exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium metabisulphite
Hydrochloric acid
Water for injection

6.2 Incompatibilities

In solutions with epinephrine, the mixture with alkaline solutions may cause a rapid degradation of the vasoconstrictor agent, as well as a greater risk of precipitation.

6.3 Special precautions for storage

Store below 25°C in the original package in order to protect from light.

6.4 Nature and contents of container

Neutral, hydrolytic class type I glass cartridges, closed on one side with a grey-coloured bromobutyl stopper and on the other side with a bromobutyl coated disc and aluminium cap.
LIDOCADREN TEVA is packed in boxes containing 50 or 100 cartridges.
Not all packages may be marketed.

6.5 Special precautions for disposal

Cartridges are for single use only.
Cartridges should not be used with other patients. The remaining of the product should be discarded.
Previously opened cartridges must not be used in other patients
Any unused product or waste material should be disposed of in accordance with local requirements.

7 REGISTRATION NUMBER: 144 03 31072

8. MANUFACTURER

Laborat ories Inibsa, S.A.,
Barcelona, Spain.

9. LICENCE HOLDER

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